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MEETING REPORT

Priority List of Research Areas for Radiological Nuclear Threat Countermeasures

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To help the nation prepare for the possibility of a terrorist attack using radiological and nuclear devices, the Office of Science and Technology Policy and the Homeland Security Council established an interagency working group. The working group deliberated on the research needs for radiological/nuclear threat countermeasures and identified and prioritized 18 areas for further attention. The highest priorities were given to research on (1) radioprotectors for use prior to exposure; (2) therapeutic agents for postexposure treatment; (3) antimicrobial therapy for infections associated with radiation exposure; (4) cytokines and growth factors; (5) mechanisms of radiation injury at the molecular, cellular, tissue and organism levels; and (6) automation of biodosimetric assays. High priority was given to (1) developing biomarkers for biodosimetry; (2) enhancing training in the radiation sciences; (3) exploring the consequences of combined injury; (4) establishing a repository of information regarding investigational countermeasures; and (5) following the health of an exposed population to better prepare for subsequent events. The research areas that the committee felt required the attention of the radiation research community are described in this report in an effort to inform this community about the needs of the nation and to encourage researchers to address these critical issues.

INTRODUCTION

To help the nation prepare for the eventuality of a terrorist attack using weapons of mass destruction, the Office of Science and Technology Policy and the Homeland Security Council established the Weapons of Mass Destruction Medical Countermeasures Subcommittee in the Spring of 2003. Their mission was the ''identification, coordination and prioritization of research, development and acquisition of medical countermeasures for biological threat agents that may be used against United States civilian population, military forces and those of our friends and allies.'' In support of that mission, an interagency working group was established to address radiological and nuclear threat countermeasures. The working group (see footnote 2) consisted of representatives from a broad range of federal agencies and included a few key individuals from academia. From this larger group, a subgroup was assembled to consider the research needs of the nation to address radiological/nuclear threat countermeasures. Described in this report are the research areas that the committee felt required the attention of the radiation research community. They are presented here in an effort to inform this community about the needs of the nation and to encourage researchers to address these critical issues. Table 1 provides a summary list of these priorities.

The research subgroup identified 18 key research areas relevant to the development of medical countermeasures against radiological and nuclear threats. Each area was as-

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signed one of four priorities: top, high, medium or low as judged by their relevance to this mission. The top priority was given to areas in which research is urgently needed to provide the best opportunities for life-saving interventions in the event of a radiological or nuclear attack. In general, higher priority was given to areas focusing on immediate, rather than delayed, consequences of radiation exposure. The priorities reflect the perceived relevance to the terrorist threat but do not represent a judgment on the intrinsic value of the research; all areas listed were deemed important to our long-term understanding of radiation injury and countermeasures. Furthermore, many research areas in radiation sciences that are not critical to radiological/nuclear threat countermeasures are and will continue to be important to the advancement of medical care and the science of the nation. The effort of the research subgroup built on the meetings and documents (*1–4*) produced by several previous working groups and committees.[3] The 18 key research areas identified by the committee are discussed below.

TABLE 1
Priority List of Research Areas for Radiological Nuclear Threat Countermeasures

Priority	Area of research
Top	Radioprotector: Pre-exposure agents
Top	Therapeutic agents: Postexposure treatment
Top	Antimicrobial agents
Top	Cytokines and growth factors
Top	Mechanisms of radiation-induced injury
Top	Biodosimetry assay automation
High	Biomarkers and devices for biodosimetry
High	Training in the radiation sciences
High	Combined injury
High	Information repository of investigational countermeasures
High	Medical follow-up of exposed populations
Medium	Progenitor cells
Medium	Decorporation therapy
Medium	Risk communication and psychological consequences
Medium	Development of animal models
Low	Mechanisms of radiation-induced carcinogenesis
Low	Epidemiology
Low	Teratogenesis and hereditary effects

RADIOPROTECTORS

Objectives:

1. To develop new agents to prevent the adverse biomedical consequences of exposure to ionizing radiation.
2. To provide strategies in conjunction with the U.S. Food and Drug Administration's (FDA) regulatory requirements to facilitate preclinical development and clinical implementation of new agents and regimens.

Priority: Top

Requirement:

In the event of a radiological/nuclear terrorist attack, it will be important to provide first responders, remediation workers and, if there is advance warning, the resident population with a radioprotector that would mitigate the effects of exposure to ionizing radiation. Ideally this agent would be long-lasting, would be easily administered, preferably orally, and would have low toxicity. Amifostine, shown in animal studies to be a radioprotector, is FDA-approved for specific consequences of radiation therapy, but it has significant side effects and a limited window of effectiveness (*5*). Other agents are in preclinical phases of development. For example, the steroid 5-androstenediol has been shown to provide moderate protection against certain radiation effects in rodents (*6, 7*). The soy isoflavone genistein and nutraceuticals including vitamin E analogs are also under investigation as possible radioprotectors (*8–10*). Much more research needs to be done. Appropriate expertise and resources must be available to conduct radiation toxicity and radiation protection experiments including concept development, drug development, long-term toxicity studies, and translation to clinical testing and application. Of significance, this area of research is applicable to oncology and to accidental occupational exposures as well as to general population exposures.

THERAPEUTIC AGENTS (POSTEXPOSURE TREATMENT)

Objective:

To develop new therapeutic agents that can be used to treat people who have been exposed to ionizing radiation.

Priority: Top

Requirement:

In the event of a terrorist attack with a radiological or nuclear device, treatment of the exposed population will be a very high priority. Treatment of minor casualties as outpatients will be necessary to ensure adequate hospital fa-

[3] Radiobiology Research Review Meeting, held in Bethesda, MD on February 26, 2003, sponsored by the National Institute of Allergy and Infectious Diseases of NIH; Molecular and Cellular Biology of Moderate Dose Radiation and Potential Mechanisms of Radiation Protection Workshop, held in Bethesda, MD on December 17–18, 2001, sponsored by the National Cancer Institute, NIH; Education and Training for Radiation Scientists Workshop, held in Bethesda, MD May 12–14, 2003, sponsored by American Society of Therapeutic Radiology and Oncology and Radiation Research Program, National Cancer Institute, NIH; Report of the Medical Preparedness and Response Subgroup of the Working Group on Radiological Dispersal Device (RDD) Preparedness, Department of Homeland Security, May 2003; Report of the Medical Preparedness and Response Subgroup of the Working Group on Radiological Dispersal Device (RDD) Preparedness, Department of Homeland Security, May 2003; Animal Experimentation at the Frontiers of Molecular, Cellular, Tissue Radiobiology, 1996, sponsored by NASA; Modifying Normal Tissue Damage Postirradiation; Report of a workshop held in Bethesda, MD on September 6–8, 2000, sponsored by the Radiation Research Program, National Cancer Institute, NIH; and Basic Research Needs for Countering Terrorism, based on a workshop held in Gaithersburg, MD on February 28 to March 1, 2002, sponsored by the Department of Energy, http://www.sc.doe.gov/bes/BES_CT_Screen_Opt.pdf.

cilities. Casualties with life-threatening infection, bleeding and gastrointestinal symptoms will require in-patient medical attention. However, people with lower exposures, of which there may be many, could receive therapeutic agents in the outpatient setting. Currently, available treatments are not optimal for administration to mass casualties, requiring intravenous administration and monitoring for severe side effects. The therapeutic armamentarium needs to be expanded.

Some classes of agents are discussed separately in this document because of the maturity of their development. However, development of new therapeutic agents need not be constrained to these categories. Possibilities exist in flavonoids, prostaglandins, steroids and nitroxides, among others (*1, 3, 11, 12*). New agents may be identified as we learn more about the mechanisms of radiation injury (*12*). Novel combinations of therapeutic agents might provide synergism, allow use of lower doses, and thereby limit side effects and/or facilitate achieving effective treatment. Combined therapies may be necessary to treat all aspects of the injury, but the interactions of the drugs must be assessed.

ANTIMICROBIAL AGENTS AFTER RADIATION INJURY

Objectives:

1. To optimize protocols for antimicrobial therapy for infections associated with radiation exposure.
2. To evaluate the physiological and cellular mechanisms that lead to infection with the goal of developing new therapeutic agents.

Priority: Top

Significance:

Infection is a primary medical complication and major cause of mortality after exposure to ionizing radiation. Antimicrobial defenses are compromised by exposure to radiation. The normal barriers to infection in the skin, airways and gastrointestinal tract are compromised, and the immune response to pathogens is reduced. The microbial flora in the gut is disrupted, local toxins are released, and pathogens can cross from the intestine into the body (translocation), leading to systemic infection that can result in shock and death.

Mortality often can be averted by administering antimicrobials to prevent or treat the infection. However, accepted antimicrobial strategies for minimizing disease in individuals with an intact immune system often are inadequate when host immune defenses and tissue integrity have been compromised by exposure to radiation (*13, 14*). The guidelines for antimicrobial therapy in febrile neutropenic patients do not apply to radiation casualties. Additional data in animals and humans are required to determine optimal therapy for radiation-related infections. Research on the physiological and cellular mechanisms that lead to infection also are necessary for the development of interventions to prevent and attenuate infections.

CYTOKINES AND GROWTH FACTORS

Objectives:

1. To obtain an FDA-approved indication for currently marketed cytokines to be used for radiation injury.
2. To develop additional cytokines and growth factors for treatment of radiation injury

Priority: Top

Requirement:

Exposure to radiation at moderate doses causes a profound decrease in cells in the bone marrow and places patients at risk of death from infection (secondary to neutropenia) or bleeding (secondary to thrombocytopenia). By stimulating the repopulation of neutrophils and thrombocytes in the bone marrow, some cytokines have been found to promote recovery in animal models (*1, 4, 15*). G-CSF (Filgrastim, Neupogen®), pegylated G-CSF (pegfilgrastim, Neulasta®), GM-CSF (sargramostim, Leukine®), and IL11 (oprelvekin, Neumega®) are now FDA-approved for the profound neutropenia and thrombocytopenia that can occur with cancer chemotherapy. An FDA indication for radiation injury does not yet exist, although many animal efficacy studies have been completed.

A limitation of G-CSF and IL11 is that they need to be administered by daily injection for an extended period. In addition, IL11 has severe toxicity. New formulations that have a prolonged effect (e.g. pegfilgrastim, which requires only one or two injections) would simplify the logistics of administration and reduce the requirement for patient follow-up in a mass casualty situation.

As demonstrated by G-CSF and IL11, cytokines and growth factors are very promising classes of compounds. Additional research is needed to advance this area and to optimize the use of cytokines and growth factors for treatment of radiation injury. Thrombopoietin (TPO), stem cell factor (SCF), and megakaryocyte growth and development factor (MDF) are currently under investigation (*1, 16–19*). Keratinocyte growth factor (KGF) shows promise for treatment of the gastrointestinal syndrome that follows radiation exposure as well as for prevention of some of the late sequelae (*1, 20, 21*). These and other agents need to be further explored, tested and developed.

MECHANISMS OF RADIATION-INDUCED INJURY

Objectives:

1. To understand the mechanisms of radiation injury at the molecular, cellular, tissue and organism levels as a basis for development of preventative, therapeutic and diagnostic approaches.

2. To develop new medical interventions and diagnostics for radiation injury.

Priority: Top

Requirement:

To prevent, treat or ameliorate radiation injury to tissue requires an understanding of the basic mechanisms of injury at the molecular, cellular, tissue and organism level. Radiation injury can manifest itself early or years after the exposure (*12, 22*). In either case, the initiating biological events that trigger the pathology and the biological events that sustain the progression must be understood. For example, understanding the biological basis for the loss of immune progenitor cells in the bone marrow will allow the logical development of interventions to mitigate the adverse effects. Increasing evidence suggests the involvement of the renin-angiotensin system in radiation nephropathy; captopril, an angiotensin-converting enzyme (ACE) inhibitor, and angiotensin II (AII) blockers show promise for treatment (*11, 23*). Pentoxifylline and tocopherol have been shown to induce regression of superficial radiation-induced fibrosis (*24*). Late-developing scarring of lung and other tissue has been untreatable, but new knowledge of the mechanisms of the development of this damage could lead to new interventions.

Only by understanding the progression from the initial radiation injury and its secondary effects to the late functional manifestations of tissue damage will effective therapeutic agents be developed (*12*). Mechanistic studies will provide new concepts about how to intervene, which could lead to more effective, less toxic interventions.

The injuries considered in this requirement include late effects of radiation that cause functional damage to tissues such as the lungs and kidneys and specifically exclude carcinogenesis, which is addressed in a separate section.

BIODOSIMETRY ASSAY AUTOMATION

Objective:

To improve, through automation, the speed and efficiency of biodosimetric assays for triage and therapy.

Priority: Top

Requirement:

If there is a radiological or nuclear incident, medical facilities will be severely burdened with people worried about their radiation exposures. Some will have received medically significant doses of radiation; others will not. All will require assessment. To handle this situation, biodosimetric systems must be rapid and efficient.

A multifaceted and integrated biodosimetry system using early physical assessments, bioindicators and biological dose assessments to aid clinical management can provide the dose estimates necessary for triage. However, despite the robustness and adaptability of existing biodosimetric approaches, the process is tedious and time-consuming with limited sample throughput. Efforts are under way to automate the biodosimetric cytogenetic analysis and to increase throughput by increasing efficiency at various steps in sample processing, preparation, analysis and reporting (*25–27*). Existing technologies can be tapped to achieve this goal. Some currently available, off-the-shelf technologies that can be applied include robotic devices for handling blood and isolating blood cells, microprocessor-controlled automated pipetting devices for transferring reagents, modules for 20 to 50 slides for simultaneous staining, and using automated instruments to ensure good laboratory practice. Biodosimetry assay automation efforts should be consistent with the relevant International Standard Organization (ISO) standards used by certified reference laboratories.

Similarly, rapid throughput for analysis of radionuclides in biological specimens is needed. In the event of a radiological incident, it will be critical to determine not only the radiation dose received but also the type and amount of internal radionuclide contamination to provide appropriate medical countermeasures. The current laboratory generally has the capability of processing tens of samples per day and requires several days to more than a week to provide results. Improved, automated systems ensuring high throughput and good laboratory practices must be developed.

BIOMARKERS AND DEVICES FOR BIODOSIMETRY

Objective:

To develop bioassays that can identify radiation-exposed individuals and that can provide individual radiation dose assessments to enable triage and optimal medical management.

Priority: High

Requirement:

In the event of a mass radiological casualty incident, new technologies will be required for rapid and early identification of those who are exposed and for accurate assessment of exposure levels. Biodosimetric tools must be available in the field as well as in hospitals.

Hematological, cytological and molecular biomarkers are radiation-responsive candidates for bioassays (*1, 11, 28*). However, work remains for complete validation of candidate radiation biomarkers over the full range of possible scenarios. Existing biodosimetry has limited usefulness at doses less than 1 Gy. Development of hand-held devices for measurement of lymphocyte counts, cytological markers, and molecular biomarkers is needed to allow deployment to the field. The throughput of both hand-held and hospital-based systems needs to be enhanced to handle mass casualties. There are opportunities to integrate the assessment of radiation exposure with the determination of

exposure to other threat agents (i.e. biological and chemical). In the long term, biomarkers may be able to predict individual risk with high sensitivity, high specificity and long-term stability, and at low cost. Such biomarkers may also serve as tools for epidemiological studies of exposed populations.

TRAINING IN RADIATION SCIENCES

Objective:

To train new scientists capable of addressing the critical research requirements described in this document.

Priority: High

Requirement:

The national capacity to foster new developments in radiation science and to translate that science to medical countermeasures for response to radiological/nuclear terrorism is limited by a shortfall in the number of appropriately trained personnel (*2, 29*). Radiation scientists will be needed to develop the medical countermeasures, to treat radiation casualties, and to provide expert advice in radiological and nuclear emergencies. The cadre of experts needs to include those trained in applied sciences such as health physics, nuclear engineering, radiation medicine, radiation safety, and dosimetry as well as the more basic sciences relevant to radiobiology.

The education and training of the next generation of radiation scientists must begin now to ensure that the necessary cadre of experts is available to meet the current and future needs of society. Opportunities need to be created for the development of new or expanded training programs. Because of the multidisciplinary nature of radiation biology, broad-based training programs such as inter-institutional consortia should be encouraged.

In the event of a radiological or nuclear terrorist attack, radiation sciences professionals will be called upon to talk to the public about health risks and available countermeasures. For these communications to be effective, it will be essential to provide scientists with the skills needed to convey complicated ideas clearly and effectively to non-specialists.

COMBINED INJURY

Objectives:

1. To understand the mechanisms of the interactions of exposures to radiation in combination with chemical agents, pathogens and traumatic injury (burn and blast).
2. To develop medical interventions for radiation injury in combination with other chemical, biological or physical exposures.

Priority: High

Requirement:

Experimental data that define the interactions of threat agents and the implications of combined exposures for treatment and prophylaxis are needed. Existing data suggest that the interaction of radiation with other injuries could produce severe medical complications (*30, 31*).

Since exposure to radiation impairs immune responses, a radiation casualty would become more susceptible to infection. Similarly, since both ionizing radiation and certain chemical warfare agents, such as sulfur mustard, cause bone marrow suppression and DNA damage, synergistic effects would be expected. Interaction of radiation injuries with physical injuries such as burns and wounds also complicates therapy. Radiation impairs the healing process and predisposes to infectious complications. Other less well-understood interactions between radiation and other exposures could complicate the pathology and medical treatment.

Because of these risks, understanding the mechanisms of interactions and developing countermeasures for combined exposures are important for full preparedness in the event of a radiological or nuclear attack.

INFORMATION REPOSITORY OF INVESTIGATIONAL RADIOLOGICAL/NUCLEAR THREAT COUNTERMEASURES

Objective:

To establish an information repository (both public and commercial confidential) of pharmaceuticals and bioassays under development as radiological/nuclear threat countermeasures.

Priority: High

Requirement:

The federal government is taking steps to facilitate the development of medical countermeasures to diagnose, prevent, mitigate or treat diseases caused by ionizing radiation related to a terrorist attack. To ensure coordinated and timely actions by the federal government to foster development of medical countermeasures for civilian biodefense, it is important that the relevant federal agencies have access to commercial confidential information and that such information be maintained by a single entity to avoid duplicative efforts.

Because of intellectual property issues, many product developers in the private sector are reluctant to make their efforts publicly available. This obstacle can be overcome by ensuring confidentiality by the federal agency that serves as the repository of information. Information would be released only to other appropriate federal agencies that have an official need to use the information and will certify that they will not release such information publicly.

Before a federal agency could formally accept this responsibility, the logistics of the proposal, the cost of the

proposal, and the availability of adequate funding for this function should be established. Since many of the logistics are already in place at the Food and Drug Administration (FDA) to protect commercial confidential information, it is a logical candidate. Other agencies with the potential to serve this function include the Department of Homeland Security, Department of Health and Human Services (National Institutes for Health), and the White House's Office of Science and Technology Policy. There may be a similar need for repositories of medical countermeasures for biological and chemical threat agents.

MEDICAL FOLLOW-UP OF EXPOSED POPULATIONS

Objective:

To follow the health outcomes of an appropriate fraction of an exposed population to evaluate the effectiveness of therapeutic measures and the correlation of health effects with dosimetry. These data will suggest modifications in medical approaches to improve emergency preparedness.

Priority: High

Requirement:

After a terrorist radiological event, there will be a population that has been exposed to a range of doses, evaluated biodosimetrically, and treated with the most up-to-date therapeutic agents. This population would provide an excellent resource for outcome studies. Biomarkers for dosimetry can be assessed over time to improve delayed dose reconstruction capabilities and to evaluate the correlations of health effects with dosimetry. By following the health of this population, information regarding the efficacy of particular interventions could be obtained. Results would be directly applicable to preparedness for subsequent events.

There are additional needs to assess the impact of interventions (prophylaxis, treatment or diagnostics) on populations and to assess the safety and efficacy of these measures. If an investigational product is administered, FDA's investigational new drug (IND) regulations require that patients be evaluated for safety and efficacy. Similarly, if a patient is given a product that was approved under FDA's ''animal rule'', confirmatory human studies are also needed. In addition to these regulatory considerations, there is also the federal government's public health mission to develop generalizable medical knowledge from these cohorts and to develop public health policy for future events.

In addition, valuable data might be obtained from retrospective studies of the impact of the interventions used to treat victims of previous radiation accidents and radiotherapy complications. For example, more than 300 persons have suffered from the acute radiation syndrome, and thousands have had local radiation injuries and burns (*32*, *33*). Although there have been some studies of the effects of the various medical interventions used for these patients or of the long-term changes in biomarkers in these people, more systemic studies could well provide valuable insights. In addition, one could critically examine the radiation oncology data on treatments given to minimize complications to determine which are effective and which would apply to the scenarios of importance here.

PROGENITOR CELLS

Objective:

To develop and assess novel approaches using progenitor cells to treat the severe loss of bone marrow cells and other organ stem cells occurring after exposure to radiation.

Priority: Medium

Requirement:

A life-threatening consequence of radiation exposure is the severe decrease in neutrophils, white blood cells produced in the bone marrow to fight infection. When these cells fall below a certain level, survival is unlikely (*1*). If the cells can be replaced, survival should be enhanced. Some of the pharmacological agents discussed elsewhere in this document stimulate the progenitors of these cells to make new cells. Another approach is to transplant bone marrow from a healthy donor. This requires careful matching of several tissue features to prevent rejection of the transplanted cells. In 1986, bone marrow transplants and fetal liver transplants were attempted in patients exposed to high doses of radiation after the accident at Chernobyl, but they were without benefit (*34*). However, relevant technologies have advanced significantly since then, and progenitor cell transplants continue to be developed for use in patients with advanced malignancies. These same technologies may benefit patients who develop acute radiation syndrome with bone marrow ablation (*4*, *11*).

Alternative progenitor cell technologies (e.g. cell banks, *ex vivo* amplification, etc.) are also in development. These approaches avoid the need to match cell types either by using the patient's own cells and amplifying them outside the body or by using cells from an early stage of development. These technologies may avoid the need for the invasive interventions required with bone marrow transplants. Much research remains to be done to develop and assess these approaches to the treatment of radiation injury.

In addition, basic research programs are needed to develop progenitor cells for other radiosensitive organs, including liver, lung, kidney, gastrointestinal tract and central nervous system.

DECORPORATION THERAPY

Objective:

To develop improved decorporation therapies and better delivery systems for chelators.

Priority: Medium

Requirement:

No significant original research to improve radioisotope chelation therapy or to identify new agents for radioisotope decorporation therapy has occurred in the U.S. in over 30 years. The DTPAs and Prussian Blue have a role in the decorporation of radioisotopes. Insoluble Prussian Blue (PB), ferric hexacyanoferrate, enhances excretion of isotopes of cesium and thallium from the body by means of ion exchange. PB is most likely to be used orally for treatment of victims of a ^{137}Cs γ-radiation dispersal device. PB is FDA-approved as 500-mg capsules and is marketed as Radiogardase™. Ca-DTPA and Zn-DTPA have recently been approved by the FDA for treating internal contamination with plutonium, americium and curium. These chelating agents generally are administered intravenously, although they can also be administered by inhalation in a nebulizer. An oral delivery system for DTPA would offer significant logistic advantages. Pediatric formulations of PB are also needed.

RISK COMMUNICATION AND PSYCHOLOGICAL CONSEQUENCES

Objectives:

1. To understand the characteristics of at-risk populations for effective communication and intervention.
2. To develop approaches to mitigate the psychological impact of a terrorist event.

Priority: Medium

Requirement:

Terrorism is specifically designed to have psychological impact. Psychological effects may well be the major consequence of a terrorist radiological event even if other medical effects are limited (*4, 35, 36*). Those most vulnerable are pregnant women, mothers of young children, children, first responders and those with prior mental illness. The anxiety and stress that result from terrorism can cause medical facilities to be overwhelmed with concerned individuals. People worried about minor symptoms are likely to flood hospitals and other health care facilities. Because of the physiological consequences of stress, an increase in the incidence of disease within the population can be expected. The psychological effects as a result of disasters, accidents and terrorist events often extend for many years after exposure. Good risk communication can go far in mitigating the fear and panic in the population. Developing effective strategies to prepare for and to respond to an event is likely to limit the psychological consequences. Research is needed to provide a greater understanding of the at-risk populations in the contexts of the individual, family, social networks, and community and to develop approaches to mitigate the psychological impact of terrorist events.

DEVELOPMENT OF ANIMAL MODELS

Objective:

To develop and validate animal models for the assessment of radiation injury and the evaluation of potential countermeasures.

Priority: Medium

Requirement:

Improved animal models are required for testing of therapeutics for treatment and prophylaxis of radiation injury (*12*). Safety and efficacy of new therapeutic agents must be demonstrated in animals before clinical trials can be initiated. Since FDA's ''animal rule'' is likely to be applied to treatments of radiation injury for determination of FDA approval, having improved animal models available is very important. Non-human primates are increasingly difficult to obtain for these assessments and in fact may not always be the best model of the human condition. In addition, animal experimentation is necessary to accurately predict the medical consequences of radiation exposure in humans and to develop new, mechanistically targeted interventions. Development of new models can provide appropriate tools to carefully assess mechanisms of radiation damage, biomarkers for biodosimetry, etc. Primates, dogs, ferrets, mice and non-mammalian species are each optimal for particular end points, but each also has limitations. Such new systems as ''humanized'' mice and genetically engineered animals might provide improved models of a human condition or expedite research efforts by providing well-defined model systems (*3, 12*). Use of a wide range of model systems may well be necessary to thoroughly address relevant questions.

MECHANISMS OF RADIATION-INDUCED CARCINOGENESIS

Objectives:

1. To understand the mechanisms of radiation-induced cellular and tissue injury that lead to cancer.
2. To develop pharmaceuticals that prevent cancers induced by radiation.

Priority: Low

Requirement:

Research on radiation-induced cancer involves microdosimetry, molecular genetics and other basic science efforts, epidemiological studies of exposed populations, and translational research to develop and implement prevention and intervention strategies.

Prevention of carcinogenesis requires an understanding of the basic mechanisms of DNA damage and repair at the molecular and cellular level. However, carcinogenesis also involves interactions among the cells in an organ or even the organism; for example, cell-to-cell communication and

whole-body homeostatic mechanisms (e.g. immune responses) can have an impact on the ultimate development of a cancer. By understanding these mechanisms, therapeutic and protective drugs might be developed that target appropriate biochemical or physiological mechanisms.

Currently a few drugs are under investigation for their ability to prevent late effects of radiation, including carcinogenesis. Amifostine and nitroxides, for example, can prevent mutagenesis in cell systems and are anticarcinogenic in rodents (*37, 38*). The applicability of these findings to humans is still unknown.

EPIDEMIOLOGY

Objective:

To conduct epidemiological studies to acquire scientific evidence regarding the long-term health effects of ionizing radiation, especially cancer.

Priority: Low

Requirement:

Radiation epidemiology is the statistical analysis of radiation effects in exposed populations, to derive correlations between the observed end point and exposure, and to generate hypotheses about possible causation. In the past, radiation epidemiology has concentrated on the observation of health effects, mainly related to cancer. Populations that have been studied extensively include atomic bomb survivors, nuclear workers, uranium miners, patients who have received medical exposure, those exposed to fallout, and those living in areas of high background radiation (*33, 39*). Ongoing epidemiological studies of various populations, especially those exposed to low-dose external and internal radionuclides, will provide information on long-term health effects in various exposure scenarios (*33, 39*).

Research is needed to improve epidemiological and biostatistical methods and models. These efforts will address the limitations in epidemiology that result from low incidence rates and long latent periods. In addition, in the longer term, biological markers of both dose and radiation-induced health effects should be developed. Recent biomedical research suggests that new end points that serve as predictors for both cancer and non-cancer outcomes might offer high sensitivity and specificity in a shorter time. One current study (*40*) is showing a distinctive molecular change in lung tissue only in workers exposed to plutonium; another (*41*) shows distinctive chromosome changes in the lymphocytes of workers exposed to neutrons, which could assist dose reconstruction. These biomarkers cannot stand alone; they need to be developed and validated. Their use after a radiological event can be useful in tracking therapeutic outcomes and predicting health consequences of radiation exposures as described above.

TERATOGENESIS AND HEREDITARY EFFECTS

Objective:

To assess the mechanisms of teratogenic and hereditary effects of exposure to radiation and to develop countermeasures for the effects.

Priority: Low

Requirement:

Teratogenesis in this context refers to malformations after *in utero* exposure to radiation. There has been extensive research on animal models and studies of the children of women who were pregnant at the time of the atomic bombings or during radiation therapy (*42*). There appears to be a threshold dose for teratogenic effects at a fetal dose of 0.1–0.2 Gy. Above this threshold, the most sensitive tissue is the central nervous system, which shows pronounced effects, especially at 8–16 weeks estimated gestational age. Development of protective agents for the *in utero* exposures would require an understanding of the mechanisms of injury and targeted therapeutics to prevent or treat the effects. With maternal exposures to radionuclides, particularly iodine and strontium, radioactive materials can transfer to the fetus; intake of these radionuclides can be minimized through standard protective actions.

Hereditary effects that are passed on to subsequent generations have been studied extensively in animal models as well as in atomic bomb survivors, radiation therapy patients, and nuclear workers. Current scientific literature suggests that the risk of hereditary effects is very low, significantly less than the risk of radiation-induced cancer.

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